

Evaluating and Comparing the Adherence to Immediate-Release Tacrolimus (Prograf®) Versus Extended-Release Tacrolimus (Advagraf®) in Kidney Transplant Recipients

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Introduction. This study compared adherence rates between immediate-release tacrolimus (Prograf®) and extended-release tacrolimus (Advagraf®) formulations in adult kidney transplant recipients in Iran. It is the first such comparison conducted in the country.

Methods. This prospective, observational cohort study was conducted among adult kidney transplant recipients in Shiraz, Iran. Adherence was assessed using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) via self-report during face-to-face or telephone interviews at baseline (month zero) and six months. Inpatient variability (IPV) of tacrolimus trough levels was calculated and compared between groups. The study also evaluated the risk factors associated with non-adherence and their potential impact on clinical outcomes.

Results. One hundred and ten patients (57 cases in the Prograf® group as twice daily; 53 cases in the Advagraf® group as once daily) completed six month follow-up. At month six, adherence rates were 63.16% in the Prograf® group versus 81.13% in the Advagraf® group ($P = .04$). Apart from correct dosing, all adherence parameters decreased significantly from baseline in both groups. The most common reason for non-adherence was forgetfulness in the Prograf® group and medication shortages/unavailability in the Advagraf® group. IPV was lower in the Advagraf® group ($13.62 \pm 8.07\%$) versus the Prograf® group ($18.15 \pm 13.18\%$), although this difference was not statistically significant ($P = .10$).

Conclusion. Extended-release tacrolimus (Advagraf®) was associated with significantly better adherence compared to the immediate-release formulation (Prograf®). These findings highlight the importance of once-daily formulations in enhancing adherence in postkidney transplantation care.

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INTRODUCTION

Kidney transplantation is the preferred modality of treatment for individuals suffering from end-stage kidney disease (ESKD). The superiority of kidney

transplantation in terms of survival compared to long-term dialysis has been extensively documented in the literature. The success of kidney transplantation significantly depends on the effective management

of immunosuppressive medication regimens post-transplantation. Non-adherence to prescribed post-transplant care protocols is significantly associated with heightened morbidity and mortality across recipients of all types of solid organ transplants. In the context of kidney transplantation, at least a clinical research has revealed a 36% incidence of graft loss and an increase in the risk of graft failure by up to seven times among non-adherent recipients when compared to those who adhered to their care protocols.¹ Multiple determinants contribute to the non-adherence of kidney transplant patients to their prescribed medication regimens.² Among these factors, the frequency of medication administration has been identified as a particularly significant contributor to non-adherence.

Calcineurin inhibitors are a pivotal part of the immunosuppressive regimen in solid organ transplantation, including the kidney. Among this class of medication, tacrolimus is currently the first-line agent. Oral formulations of tacrolimus are available as immediate-release (e.g., Prograf®) and extended-release (e.g., Envarsus®, Astagraf® [in the USA], Advagraf® [in Europe]).³ Prograf®, the immediate-release formulation, requires dosing twice daily; on the other hand, Advagraf® is an extended-release formulation that is taken once daily. Studies have shown that conversion from Prograf® to Advagraf® can significantly improve drug adherence among transplant patients. This is largely due to the reduced dosing frequency, which simplifies patients' medication regimens and fits better into their daily lives.⁴⁻⁶ Improved adherence is crucial in this population as it directly correlates with better graft survival and patient outcomes. By enhancing the convenience of the immunosuppressive regimen, Advagraf® represents a meaningful advancement in the management of transplant patients.⁷

Despite the theoretical advantages of once-daily tacrolimus, its impact on adherence and intra-patient variability (IPV) in middle-income countries with distinct medication access challenges remains poorly characterized. High tacrolimus IPV, which is closely linked to non-adherence, is associated with poor graft outcomes including late rejection and graft failure in kidney transplantation.⁸ In contrast, adherent patients had low tacrolimus IPV and more favorable clinical outcome like lower risk of antibody-mediated rejection and BK viremia in

kidney transplantation.⁹

A randomized controlled trial using electronic monitoring in renal transplant recipients have shown that once-daily compared with twice-daily tacrolimus regimen had significantly higher treatment persistent among patients (88.2% vs. 78.8%, $P = .0009$).¹⁰ On the other hand, at least a systematic review and meta-analysis on 12 studies comprising 2,410 patients demonstrated that once-daily tacrolimus and twice-daily immediate-release tacrolimus provide comparable safety, efficacy, and pharmacokinetic exposure in adult kidney transplant recipients. Notably, dose implementation has been better with once-daily tacrolimus.¹¹

Despite these findings, prior research in Iran could not evaluate formulation-related adherence because extended-release tacrolimus was unavailable. This tacrolimus formulation was introduced into the Iranian pharmaceutical market about four years ago, and its administration has commenced among liver and kidney transplant recipients across transplant centers nationwide. On the other hand, non-adherence rates in Iranian kidney transplant recipients have been reported as high as 55%.¹² This study therefore addresses a critical gap by evaluating whether once-daily tacrolimus improves adherence and reduces IPV in the real-world context of Iranian kidney transplant care, where medication access and distribution pose unique challenges.

METHODS

Study Design and Setting

This is a prospective observational cohort study conducted over a one-year period from July 2022 to July 2023. Patients were followed for six months to assess adherence to their assigned tacrolimus formulation. The investigation was conducted in the Abu-Ali Sina Organ Transplant Center and Mottahari specialty and subspecialty polyclinic, both of which are affiliated to Shiraz University of Medical Sciences, and also the private office of the attending nephrologists. The Medical Ethics Committee of Shiraz University of Medical Sciences approved the study (ID: REC.SUMS 1401.400). All recruited patients were given their written and signed consent forms.

Patient selection

The study population included all adult kidney

transplant recipients who met certain eligibility criteria. The inclusion criteria were as follows: 1) age 18-64 years, 2) first time of kidney transplantation, 3) duration of kidney transplantation at least six months, 4) receiving oral formulation of tacrolimus as part of the immunosuppressive regimen (either Prograf® or Advagraf®), and 5) giving written permission as consent form to participate in the study. The rationale behind considering at least six months from transplantation and tacrolimus treatment was reaching a stable status of immunosuppressive therapy in the cohort. Patients with variable tacrolimus doses within the recent one month, receiving other brand names of tacrolimus oral formulation available in the Iranian pharmaceutical market such as Suprotac® or Cograft®, using Advagraf® as a *de novo* approach (starting immediately after transplantation), simultaneous pancreas or liver transplantation, and having incomplete documentation and clinical/laboratory data during the follow-up period were excluded. Individuals who experienced acute rejection during the first month of the study were also considered ineligible. Conversion from twice daily (Prograf®) to once daily tacrolimus (Advagraf®) dosing was done on an equivalent 1:1 (mg:mg) total daily dose basis. Patient assignment to receive either Prograf® or Advagraf® was based on clinical practice and medication availability at the time of enrollment. All patients had been stabilized on their respective tacrolimus formulations for at least one month prior to study entry.

Data Collection

Required data were collected through face-to-face interviews with patients and reviewing medical records available in the electronic database in the hospital information system. They included the following variables: demographic data (age, sex), socio-economic-cultural characteristics (marital status, place of residence, type of accommodation, education level, employment status, average monthly income, type of insurance), habitual history (smoking, alcohol or drug addiction), clinical, laboratory, and transplant-related data (type of donor, time since transplantation, cause of chronic kidney disease (CKD), duration and type of dialysis before transplantation, co-morbidities, history of acute rejection, serum creatinine level as well as eGFR based on the CKD-EPI 2021 formula at the

time of transplantation,¹³ month zero (study entry), and month six, immunosuppressive drug regimen, and other medications received, and tacrolimus trough level). Measurement of tacrolimus plasma levels was performed at the baseline (study entry), four weeks, and six months thereafter.

Assessment of Patient Adherence

The adherence to Prograf® and Advagraf® in the cohort was determined through self-reporting using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS). BAASIS is a self-report questionnaire used by the Basel Adherence Research Group to assess adherence to immunosuppressive medications.¹⁴ This scale consists of four questions regarding the taking-medication dimension, medication holidays, dose reduction, and continuity of intake within one month (Table 1). A positive response to any of these questions indicates non-adherence to Prograf® or Advagraf® in the past month. Adherence was assessed at two time points, including month zero and month 6 after baseline, through face-to-face interviews or telephone calls. The possible reasons for non-adherence reported by the patients were also recorded.

Calculation of Tacrolimus Dose to Concentration Ratio

Based on tacrolimus trough levels at baseline (study entry), four weeks, and six months, and considering the corresponding daily doses taken by patients, the dose-to-trough concentration ratio was calculated for both Prograf® and Advagraf® recipients at the three time points.

Table 1. Basel Assessment of Adherence to Immunosuppressive Medications Scale

Component	Criterion for non-adherence
1. Do you recall not taking your tacrolimus capsules at any time during the past 4 weeks?	If any of the questions were answered with "yes"
2. Have you skipped several consecutive doses of tacrolimus during the past 4 weeks?	
3. Do you recall taking your tacrolimus capsules more than 2 h from the prescribed dosing time during the past 4 weeks?	
4. Have you reduced the prescribed amount of your tacrolimus capsules during the past 4 weeks?	

Calculation of Tacrolimus Intra-patient Variability (IPV)

IPV is defined as the fluctuation in tacrolimus concentration in an individual over a specified period of time when the tacrolimus dose remains unchanged. It was calculated by using tacrolimus drug concentrations at three time points (zero, one month, and six months later) based on the following formula:¹⁵ $CV\% = (\text{Standard deviation} / \text{Mean}) \times 100$

Statistical Analysis

The normal distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. The mean and standard deviation (SD) and median (interquartile range) were utilized to report normally and non-normally distributed quantitative variables, respectively. On the other hand, frequency and percentage were used to express qualitative data. Independent sample t-test and Mann-Whitney test were employed to compare the quantitative variables between two groups (adherent and non-adherent) with normal and non-normal distribution, respectively. Qualitative variables between adherent and non-adherent subjects were compared by using the Chi-square or Fisher's exact test. The possible association between adherence to Prograf® or Advagraf® and different quantitative/qualitative variables was performed by logistic regression analysis with odds ratio (OR) and 95% confidence interval (CI) via a stepwise method. *P*-values less than 0.05 were considered statistically significant. Multivariable logistic regression analysis was performed using the enter method, including all variables with *P* < .20 in univariate analysis. Variables included were: age, tacrolimus formulation, number of medications, living condition, smoking history, and alcohol consumption history. Adjusted OR and 95% CI were reported. All the above statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 26.0.

RESULTS

General Characteristics

One hundred and twenty patients were primarily screened. Ten individuals were excluded from the study due to receiving a second kidney transplant or medication shortage, resulting in the final number of 110 patients for evaluation. In this

study, 57 subjects received twice-daily (Prograf®) and 53 patients received once-daily (Advagraf®). Information regarding the demographic, clinical, and socio-economic-cultural characteristics of all patients is shown in Table 2. More than half of the cohort (54.5%) were males. The participants' age ranged between 20 and 64 years. Most of the subjects (94.5%) received a transplanted kidney from a deceased donor. The level of education and employment status of about one-third of the study population were diploma and housekeeper, respectively. More than three-fourths (79.1%) of the study population were receiving hemodialysis before transplantation. The median (interquartile range) duration of dialysis before transplantation was 18.23 (16.37) months. The transplantation duration in the cohort ranged from 7 to 300 months. The most common cause of ESKD was hypertension. Hypertension was also the most frequent co-morbidity in the cohort.

Patient Adherence to Prograf® & Advagraf®

Based on the BAASIS criteria, 42 patients (73.68%) in the Prograf® group and 38 patients (71.70%) in the Advagraf® group were adherent at baseline (month zero), which was comparable between the two groups (*P* = .72). After six months, 36 (63.16%) and 43 (81.13%) patients in the Prograf® and Advagraf® groups were identified to be adherent to the tacrolimus regimen, respectively; the difference was statistically significant (*P* value = .04). These comparisons are demonstrated in Table 3.

Almost all patients (99%) had sufficient motivation to continue treatment. One-fourth of the cohort (25.4%) had assistance in using tacrolimus, with spouses being the primary caregivers. Approximately one-third (33.63%) of the study population reported using reminders; the alarm clock was the most commonly used aiding tool. According to the patients' statements, the most common reason for non-adherence with Prograf® and Advagraf® was forgetfulness and medication shortages/unavailability, respectively.

Regardless of the treatment group (Prograf® and Advagraf®), except for the correct dose, other adherence parameters were statistically significantly lower after six months than at baseline (month zero) (Figure 1).

According to Table 4, by considering treatment groups, the "taking dimension (drug dose

Table 2. Demographic, clinical, and socioeconomic-cultural characteristics of the study population (N = 110)

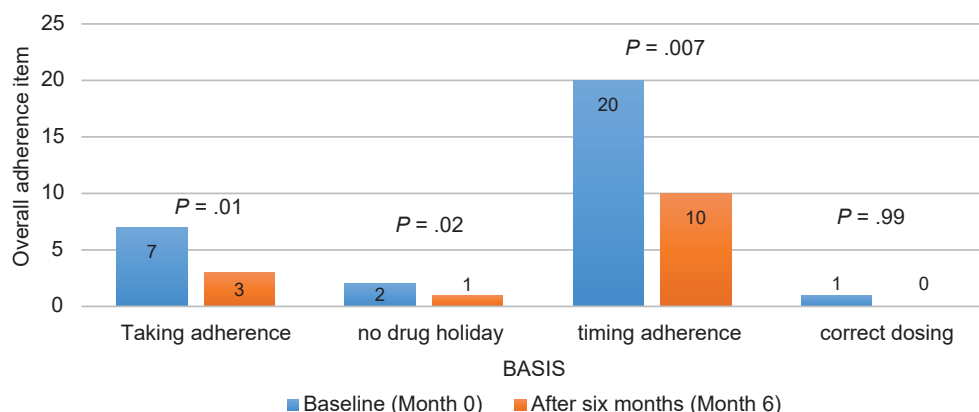
Variable	Total (n=110)	Prograf® (n=57)	Advagraf® (n=53)	P
Gender (%)				
Male	60 (54.5)	34 (59.65)	26 (49.06)	.34
Female	50 (45.5)	23 (40.35)	27 (50.94)	
Age (years)				
Mean ± Standard Deviation	44.72 ± 12.89	41.88 ± 12.04	47.76 ± 13.18	.19
Causes of End Stage Kidney Disease (%)				
Hypertension	30 (27.3)	17 (29.82)	13 (24.53)	.21
Diabetes	12 (10.9)	5 (8.77)	7 (13.21)	
Glomerulonephritis	29 (26.4)	11 (19.29)	18 (21.69)	
Others	39 (35.5)	24 (42.11)	15 (28.3)	
Co-morbidities (%)				
Hypertension	30 (27.3)	17 (29.82)	13 (24.53)	.31
Diabetes	21 (19.1)	12 (21.05)	9 (16.98)	
Type of Dialysis before Transplantation (%)				
Hemodialysis	87 (79.1)	44 (77.19)	43 (81.13)	.39
Peritoneal	23 (20.9)	13 (22.81)	10 (18.87)	
Education level (%)				
Illiterate	32 (30.1)	15 (26.32)	17 (32.08)	.74
School grade	55 (51.88)	28 (49.12)	27 (13.21)	
Academic grade	19 (17.92)	11 (19.29)	8 (15.09)	
Unknown	4 (3.64)	3 (5.26)	1 (1.89)	
Marital status (%)				
Married	82 (76.63)	40 (70.18)	42 (79.25)	.10
Single	23 (21.49)	16 (28.07)	7 (13.21)	
Separated/Divorced	2 (1.86)	1 (1.75)	1 (1.89)	
Unknown	3 (3.64)	0 (0)	3 (5.66)	
Living condition (%)				
With Family	101 (94.39)	49 (85.96)	52 (98.11)	.11
Alone	6 (5.6)	5 (8.77)	1 (1.89)	
Unknown	3 (2.73)	3 (5.26)	0 (0)	
Substance use (%)				
Never	105 (97.22)	53 (92.98)	52 (98.11)	.51
Current or previous	3 (2.7)	2 (3.51)	1 (1.89)	
Unknown	2 (2.73)	2 (3.51)	0 (0)	
Alcohol use (%)				
Never	107 (98.16)	55 (96.49)	52 (98.11)	.74
Current or previous	2 (1.8)	1 (1.75)	1 (1.89)	
Unknown	1 (0.91)	1 (1.75)	0	
Smoking (%)				
Never	101 (91.81)	51 (89.47)	50 (94.34)	.39
Current or previous	8 (7.27)	5 (8.77)	3 (5.66)	
Unknown	1 (0.91)	1 (1.75)	0 (0)	
Duration of transplantation (months)				
Range	7-180	7-96	8-108	.10
Mean ± Standard Deviation	44.82 ± 42.48	35.36 ± 23.89	54.96 ± 54.42	
Number of administrated medications				
Range	3-8	3-8	3-8	.65
Mean ± Standard Deviation	4.92 ± 1.83	5.01 ± 1.87	4.83 ± 1.79	
Monthly Income (%)				
Less than 15 United States dollars	11 (10)	5 (8.77)	6 (11.32)	.91
Between 15-85 United States dollars	32 (29.09)	17 (29.82)	15 (28.3)	
More than 85 United States dollars	63 (57.27)	33 (57.89)	30 (56.6)	
Unknown	4 (3.6)	2 (3.51)	2 (3.77)	

The percent for each variable was calculated by dividing its value by the number of patients in the same column (n= 110, 57, or 53).

Table 3. The level of patient adherence to tacrolimus (Prograf® and Advagraf®) at baseline and after 6 months

Adherent	Prograf® (N=57)	Advagraf® (N=53)	Total	P
At baseline (Month 0)				
Yes (%)	42 (73.68)	38 (71.7)	80 (72.73)	.72
No (%)	15 (26.32)	15 (28.3)	30 (27.27)	
After six months (Month 6)				
Yes (%)	36 (63.16)	43 (81.13)	79 (71.82)	.04
No (%)	21 (36.84)	10 (18.87)	31 (28.18)	

The percent for each variable was calculated by dividing its value by the number of patients in the same column (n = 57, 53, or 110).

**Figure 1.** Comparison of different items of adherence to tacrolimus, regardless to its formulation, at baseline (month 0) and six months later (month 6).

forgetting)” factor from the BAASIS was significant in both the Prograf® and Advagraf® groups after six months ($P = .004$ and $P = .01$, respectively). In terms of the “timing dimension (more than two hours delay in drug consumption)” factor, there was a statistically significant difference in the Prograf® group ($P = .03$), but not in the Advagraf® group after 6 months ($P = .07$).

Associated factors of patient non-adherence to Prograf® & Advagraf®

According to univariate logistic regression analysis, there was a significant association between tacrolimus adherence and patient age (OR: 1.05, 95%CI: 1.01-1.09), the number of co-administered medications (OR: 1.19, 95%CI: 1.02-1.39), type of residence (OR: 0.37, 95%CI: 0.16-0.86; $P = .02$), smoking (OR: 0.18, 95%CI: 0.04-0.86; $P = .02$), alcohol consumption (OR: 0.11, CI: 0.01-0.94), and tacrolimus formulation (OR: 2.41, 95%CI: 1.03-5.64) (Tables 5 & 6). Multivariable logistic regression analysis, adjusting for potential confounders including age, number of medications, living condition, and smoking, confirmed that Advagraf® use was independently associated with higher

adherence (adjusted OR: 2.38, 95% CI: 1.01-5.62, $P = .048$). Age remained significantly associated with adherence (adjusted OR: 1.04, 95% CI: 1.00-1.08, $P = .049$). (Table 7)

Clinical Outcome

Acute Rejection. During the six-month observation period, the frequency of acute rejection episodes was lower in the Advagraf® (n = 1) group than in the Prograf® group (n = 4). However, this difference did not reach statistical significance ($P = .2$).

Mortality. There was no reported mortality in either Advagraf® or Prograf® group during the follow-up period (6 months).

Kidney function tests. Baseline serum creatinine level was comparable between Prograf® and Advagraf® groups ($P = .5$). Compared with baseline values (month zero), both groups experienced a reduction in mean serum creatinine levels at month six. The decrease was more pronounced in the Advagraf® group than in the Prograf® group (0.19 mg/dl and 0.04 mg/dl, respectively); however, this difference was not statistically significant. Similarly, the eGFR was comparable between the

Table 4. Adherence to tacrolimus (Prograf® and Advagraf®) at baseline and after 6 months based on different items of the BAASIS

Tacrolimus Formulations	At Baseline	After Six Months			P
		Yes	No	Total	
Forgetting drug dose					
Prograf®	Yes	1	1	2	.004
	No	2	53	55	
	Total	3	54	57	
Advagraf®	Yes	2	6	8	.01
	No	1	44	45	
	Total	3	50	53	
Forgetting consecutive drug doses					
Prograf®	Yes	0	57	57	NA
	No	0	57	57	
Advagraf®	Yes	1	2	3	.40
	No	0	50	50	
	Total	1	52	53	
More than two hours delay in drug consumption					
Prograf®	Yes	6	9	15	.03
	No	6	36	42	
	Total	12	45	57	
Advagraf®	Yes	4	11	15	.07
	No	3	35	38	
	Total	7	46	53	
Correct drug consumption					
Prograf®	Yes	0	0	0	NA
	No	1	56	57	
	Total	1	56	57	
Advagraf®	Yes	0	0	0	NA
	No	1	52	53	
	Total	1	52	53	

NA: not assessed

Table 5. The possible association of quantitative factors with adherence to tacrolimus (Prograf® and Advagraf®) in the study population after six months

Variable	Mean± Standard Deviation	P	OR (95% Confidence Interval)
Age (Years)			
Adherent	46.4 ± 13.2	.02	1.05 (1.01-1.09)
Non-adherent	40.38 ± 11.53		
Duration of Transplantation (Months)			
Adherent	44.45 ± 45.21	.7	1.1 (0.93-1.50)
Non-adherent	42 ± 0.62		
Number of Underlying Diseases			
Adherent	0.68 ± 0.67	.3	0.78 (0.41-1.141)
Non-adherent	0.54 ± 0.62		
Duration of Dialysis before Transplantation (Months)			
Adherent	18.58 ± 17.15	.7	2.99 (0.16-5.65)
Non-adherent	17.32 ± 14.44		
Number of Medications Used			
Adherent	5.32 ± 7.1	.02	1.19 (1.02-1.39)
Non-adherent	4.55 ± 1.42		

two groups at baseline. After six months, eGFR increased in both groups; however, the difference in eGFR between Prograf® and Advagraf® recipients

after six months was not statistically significant ($P = .5$).

Other Clinical & Laboratory Variables.

Table 6. The possible association of qualitative factors with adherence to tacrolimus (Prograf® and Advagraf®) in the study population after six months

Variable	Adherent to Tacrolimus Regimen (79 patients)	Non-adherent to Tacrolimus Regimen (31 patients)	P	OR (95% Confidence Interval)
Type of Tacrolimus Formulation (%)				
Prograf®	37 (33.63)	21 (19.09)	.04	2.41 (1.03-5.64)
Advagraf®	42 (38.18)	10 (9.09)		
Type of Residence (%)*				
Tenant	60 (54.54)	14 (12.72)	.02	0.37 (0.16-0.86)
Landlord	19 (17.27)	13 (11.81)		
Smoking (%)*				
Never	76 (69.09)	25 (22.72)	.03	0.18 (0.04-0.86)
Past or Current	3 (2.72)	5 (4.54)		
Alcohol Consumption (%)*				
Never	79 (71.81)	28 (25.45)	.02	0.11 (0.01-0.94)
Past or Current	0 (0)	2 (1.81)		
Substance abuse (%)*				
Never	78 (70.90)	27 (24.54)	.1	0.17 (0.02-1.99)
Past or Present	1 (0.90)	2 (1.81)		
Gender (%)				
Male	45 (40.90)	15 (13.63)	.41	0.7 (0.31-1.63)
Female	34 (30.90)	16 (14.54)		
ESKD Cause (%)				
Hypertension	23 (20.91)	7 (6.36)	.62	0.7 (0.27-1.88)
Diabetes	10 (9.09)	2 (1.81)		
Glomerulonephritis	20 (18.18)	9 (8.18)		
Other	26 (23.63)	13 (11.81)		
Marital Status (%)*				
Married	64 (58.18)	20 (18.18)	.2	0.58 (0.22-1.58)
Single	15 (13.63)	8 (7.27)		
Education Level (%)*				
Illiterate	28 (25.45)	4 (3.63)	.1	1.9 (0.68-5.63)
Primary Education	39 (35.45)	16 (14.55)		
Academic Education	12 (10.90)	7 (6.36)		
Living Situation (%)*				
With Family	74 (67.27)	27 (24.54)	.5	1.82 (0.20-16.34)
Alone	5 (4.54)	1 (0.90)		
Place of Residence (%)*				
Inside Shiraz City	44 (40)	17 (15.45)	.5	1.3 (0.55-3.32)
Outside Shiraz City	35 (31.81)	10 (9.09)		
Monthly income (%)*				
Less than 15 United States Dollars	9 (8.18)	2 (1.81)	.8	1 (0.41-2.46)
Between 15-85 United States Dollars	23 (20.90)	9 (8.18)		
More than 85 United States Dollars	47 (42.72)	16 (14.54)		

*There is some missing data for these variables. Therefore, the sum in each column is less than expected (79 or 31 patients). The percent for each variable was calculated by dividing its value by the total number of patients (n = 110).

Regarding IPV over a six-month duration, IPV in the Advagraf® group was lower than in the Prograf® group ($13.62 \pm 8.07\%$ and $18.15 \pm 13.18\%$, respectively); however, this difference did not reach statistical significance ($P = .1$). Moreover, although the IPV value was lower in the adherent group ($14.69 \pm 10.91\%$) compared to the non-

adherent group ($20.94 \pm 12.02\%$) after six months, this difference was also not statistically significant ($P = .7$). In addition, the tacrolimus trough level, mean daily dose, and dose/trough concentration ratio were comparable between the Advagraf® and Prograf® groups at baseline, month one, and month six (Table 8).

Table 7. Multivariable Logistic Regression Analysis of Factors Associated with Tacrolimus Adherence in the study population after six months

Variable	Adjusted OR (95% Confidence Interval)	P
Tacrolimus formulation (Advagraf® vs. Prograf®)	2.38 (1.01-5.62)	.048
Age	1.04 (1.00-1.08)	.049
Number of Medications	1.15 (0.98-1.35)	.09
Living Condition (with family vs. alone)	0.42 (0.15-1.18)	.10
Smoking (never vs. ever)	0.22 (0.04-1.21)	.08

DISCUSSION

Numerous studies have highlighted that adherence to an immunosuppressive treatment regimen is crucial for preserving organ function and longevity, as well as preventing rejection

following solid organ transplantation. To improve patient adherence, several strategies have been proposed, with medication regimen simplification standing out as a notable approach.¹⁶ One of these simplification methods involves converting from twice-daily tacrolimus to a once-daily regimen, thereby reducing the frequency of daily medication intake and offering a practical solution to enhance patient adherence and potentially improve transplant outcomes.¹⁷ In this preliminary study, for the first time among kidney transplant recipients in Iran, we demonstrated that patients treated with Advagraf® were significantly more adherent compared to those on Prograf® over six months, along with lower IPV levels.

In our cohort, the rate of non-adherence after conversion observed six months later was 28.18% (36.84% in the Prograf® group and 18.87% in the

Table 8. The comparison of different clinical and laboratory parameters between Prograf® and Advagraf® recipients at the baseline and after 6 months

Variable	Tacrolimus Formulations	Mean ± Standard Deviation	P
Serum Creatinine level, mg/dl	Prograf®	1.50 ± 1.09	.5
	Advagraf®	1.4 ± 0.65	
	Prograf®	1.46 ± 1.36	.2
	Advagraf®	1.21 ± 0.37	
eGFR, ml/min/1.73m ²	Prograf®	68.26 ± 20.35	.1
	Advagraf®	62.6 ± 20.33	
	Prograf®	72.74 ± 19.9	.5
	Advagraf®	70.34 ± 21.01	
Tacrolimus Trough level, ng/ml	Prograf®	6.55 ± 2.43	.5
	Advagraf®	6.32 ± 2.17	
	Prograf®	5.42 ± 2.4	
	Advagraf®	7.35 ± 4.44	
	Prograf®	5.80 ± 2.37	
	Advagraf®	5.94 ± 1.95	
Tacrolimus Mean Daily Dose, mg/day	Prograf®	2.39 ± 1.41	.9
	Advagraf®	2.51 ± 1.51	
	Prograf®	2.39 ± 1.41	
	Advagraf®	2.41 ± 1.51	
	Prograf®	2.30 ± 1.27	
	Advagraf®	2.27 ± 1.41	
Tacrolimus Dose/Trough Concentration Ratio	Prograf®	0.36	.4
	Advagraf®	0.4	
	Prograf®	0.42	
	Advagraf®	0.33	
	Prograf®	0.38	
	Advagraf®	0.39	

Advagraf® group); this difference was statistically significant between the two groups after six months. While our findings demonstrate superior adherence with Advagraf®, the existing literature is notably heterogeneous, with several studies reporting discordant results. In a Norwegian multicenter observational study, adherence improved transiently one month after conversion from Prograf® to Advagraf® (58.1% vs. 46.8%) but returned to baseline levels by three, six, and 12 months (33.3–44%).¹⁸ Similarly, a Swedish survey across 15 centers found no significant difference in adherence between twice-daily and once-daily tacrolimus at baseline or after 12 months using the BAASIS criteria.¹⁹ In Germany, a multicenter non-interventional study reported a non-adherence rate of 67.7% at 18 months post-conversion, suggesting that once-daily dosing (Advagraf®) alone may not sustain long-term adherence.²⁰ A Canadian randomized controlled trial, however, demonstrated significantly higher adherence with once-daily dosing over four months using electronic monitoring and pharmacy refill data,²¹ aligning with our findings.

Several factors may explain these discordant results. First, follow-up duration varies considerably across studies; our six-month follow-up may capture a period of maximum benefit before adherence behaviors plateau or decline. Second, differences in healthcare systems, medication access, and patient education may modulate the impact of formulation on adherence. Third, methods used to assess adherence (self-report vs. electronic monitoring vs. pharmacy refill) have different sensitivities and specificities, which may account for some of the variability. Fourth, patient selection criteria and baseline adherence levels differ across studies, potentially confounding results. These considerations underscore the need for standardized adherence assessment tools and longer follow-up in future research.

Notably, the likelihood of non-adherence underreporting based on self-reported methods such as patient interviews (like the BAASIS used in this study) is considerably higher than that of objective methods such as pill counting or serum drug level measurement. This suggests that the actual rate of non-adherence to tacrolimus formulations in the current study (Prograf® or Advagraf®) may be even higher than the reported 27.27% or 28.18%.

Therefore, in addition to the BAASIS, measurable indices such as the IPV and the dose-to-trough concentration ratio (as measurable criteria) of tacrolimus were also determined and compared between the two groups in the current study. In this regard, the IPV value in the Advagraf® group was lower than that in the Prograf® group (13% vs. 18%, respectively), but this difference was not statistically significant. Similarly, the dose/trough concentration ratio was comparable between the Advagraf® and Prograf® groups in the present survey. Recent data have indicated that a high IPV has detrimental effects on allograft survival. The primary clinical factor associated with high tacrolimus IPV is medication non-adherence, which is very common among solid organ recipients.²² The development of software to assist with remote monitoring and medication dosing could help improve tacrolimus IPV in solid organ recipients. In a retrospective study by Larpparisuth *et al.* in 53 kidney transplant patients in Thailand, IPV did not change significantly after switching from twice-daily to once-daily tacrolimus, and the difference was not statistically significant at baseline and after six months (17.46% vs. 14.83%, respectively).²³ Factors other than dosing frequency—including pharmacogenetics (CYP3A5 genotype), ethnicity, food-drug interactions, diarrhea, and liver disease—may influence IPV more than formulation alone.^{15,24} Our study may not have enough statistical power to detect small but clinically meaningful differences in IPV, and the borderline *P*-value (.10) may reflect a type II error rather than a true absence of effect.

According to the patients' statements, the most common reasons for non-adherence to tacrolimus in the Prograf® and Advagraf® groups in the present study were forgetfulness and medication shortage/difficulty in access, respectively. Similarly, Moradi *et al.* reported forgetfulness as the most prevalent reason declared by the participants for non-adherence to immunosuppressive regimen including immediate-release tacrolimus in kidney transplant recipients at the same setting.¹² According to another study in Mashhad, Iran, barriers to immunosuppressant adherence in kidney transplant recipients are concurrent use of many immunosuppressive agents, lack of knowledge about the usefulness of immunosuppressive medications, confusion about taking the medication, and difficulty in remembering the medication

used.²⁵ These results suggest that the use of once-daily tacrolimus formulations could help in reducing the possibility of forgetfulness and improving adherence in kidney transplant recipients. The problem of Advagraf® shortage/difficulty in access is mostly because this medication is not currently manufactured in our country and is completely imported from Europe. This issue can be partially dealt with by having a more appropriate timeline for persistent drug distribution and involving more pharmacies across the city in providing Advagraf® to kidney transplant recipients.

Regarding clinical outcomes, the current study showed that although the number of acute rejection episodes during the follow-up period in the Advagraf® group was lower than in the Prograf® group, this difference did not reach statistical significance. Similarly, serum creatinine levels and eGFR of the patients after six months were lower and higher, in the Advagraf® group than the Prograf® group, respectively. However, these differences between the two groups were neither clinically (all eGFR values were above 60 ml/min/1.73m²) nor statistically significant (*P* values > .05). Various studies have examined the efficacy and one-year graft survival for both once-daily (Advagraf®) and twice-daily (Prograf®) tacrolimus formulations.^{26,27} For example, according to Kramer *et al.*'s study on kidney transplant patients' data from several European countries in two clinical trials, the number of biopsy-confirmed graft rejection episodes over one year in recipients of the twice-daily (Prograf®) and once-daily (Advagraf®) tacrolimus formulations was comparable (14.1% and 13.9%, respectively).²⁶

Our findings should be interpreted with caution since the present study have certain limitations, as follows: The lower number of patients in the Advagraf® group compared to the Prograf® group. On the other hand, the calculated statistical power is 68%, possibly resulting in an underpowered study and type II error. This issue was mostly related to the transient shortage of Advagraf® in Iranian pharmaceutical market and passing the expiration date of certain dosage forms of Advagraf®; short term follow-up period of patients (only six months) precluded evaluating the one-year survival rates of patients and their transplanted kidneys; not evaluating and comparing common/serious side effects of the tacrolimus in Prograf® and Advagraf® recipients (such as gastrointestinal disorders,

neurotoxicity, nephrotoxicity, new-onset diabetes, hair loss); the lack of formal randomization and the non-random assignment of patients to treatment groups also represents a significant limitation. While demographic and clinical characteristics were comparable between groups at baseline, we cannot exclude the possibility of unmeasured confounding variables that may have influenced both treatment assignment and adherence outcomes.

CONCLUSION

Findings of the current study show that adherence levels, as determined by the BAASIS criteria and based on self-reports, were significantly higher in the Advagraf® group compared to the Prograf® group in adult kidney transplant recipients after six months. In addition, IPV in the Advagraf® group was lower than that in the Prograf® group, although this difference was not statistically significant. Type of tacrolimus formulation (twice-daily dosing, Prograf®) was significantly associated with non-adherence to the tacrolimus regimen. However, these results should be reproduced in larger studies comprising several centers across the nation with an adequate follow-up period and addressing both clinical effectiveness as well as safety of Prograf® and Advagraf®.

STATEMENTS & DECLARATIONS

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Conflict of Interest

None.

Author Contributions

M.S. contributed to study design & conceptualization, supervision, clinical interpretation of results, and manuscript review. M.M.M, M.D, and I.A. were involved in data analysis and manuscript drafting. M.M. performed patient selection, data gathering, and assessment of patient adherence. J.R. was involved in patient selection and clinical interpretation of results. N.R. was involved in patient selection and clinical interpretation of results. I.K. contributed to study design, study supervision, funding acquisition, clinical interpretation of results, and manuscript

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Consent for publication

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